REMARKS/ARGUMENTS

With entry of this amendment, claims 23-37 are pending in the above-identified application. Claim 37 has been amended. The amendment to Claim 37 provides antecedent basis for a patient. No new matter has been added by this amendment. Applicants respectfully request reconsideration of the application light of the above amendments and the following remarks.

Rejections Under 35 U.S.C. §103

Claims 23, 31-32, 33-37 stand rejected under 35 USC §103(a) as being obvious over Sallusto *et al.*, 1994 (*J. Exp. Med.* 179:1109-1118, of record), in view of Bigotti *et al.*, 1991 (*Prostate* 19:73-87, newly cited), as evidenced by Inaba *et al.*, 1987 (*J. Exp. Med.* 166:182-194, of record). The Examiner has summarized Sallusto *et al.* as teaching that exposure to GM-CSF plus IL-4 converts blood mononuclear cells to immature dendritic cells, that maintain the antigen capturing and processing capacity characteristics of immature dendritic cells *in vivo* and efficiently present soluble antigen, such as tetanus toxoid to specific T cell clones (abstract). Sallusto *et al.* is also asserted as teaching that dendritic cells (DCs) exist in two stages of maturation and teaching that as immature dendritic cells, they are capable of antigen capture/processing and immunostimulation, but as the dendritic cells mature, they lose antigen-capturing capacity (p. 1109). Sallusto *et al.* is further asserted as teaching that Langerhans cells represent immature dendritic cells in skin (p. 1109, first column, first two lines of second paragraph). Sallusto *et al.* also is believed by the Examiner to teach that the dendritic cells are from human peripheral blood (p. 1110, first column, line 6 of second paragraph). The Examiner admits that Sallusto *et al.* does not teach that the antigen is a prostate antigen or that the activation of T cells specific for prostate antigen is 2 to 3 fold more than that of the control.

Bigotti *et al.* is cited by the Examiner as teaching that Langerhans cells (LCs) are a type of dendritic cells capable of direct prostate antigen presentation to immune cells. The LCs are also asserted to be able to elicit the immune response and for providing a means for

controlling the escape of cancer cells from the immune surveillance (abstract, p. 85). Bigotti *et al.* is also said by the Examiner to teach that Langerhans cells are found mainly in low grade prostate cancer, as opposed to the higher grades, and that the LCs represent a good prognostic indicator (abstract). Bigotti *et al.* is also asserted to teach that the number of Langerhans cells is directly correlated with the expression of HLA class II-DR molecules of tumor cells, and that Langerhans cells and HLA class II molecules provide a means of eliciting the immune response. Further, the Examiner alleges that Bigotti *et al.* teach that it is commonly believed that the antigen presenting properties are dependent upon HLA class II expression (p. 74, 4th paragraph).

Based on the above summary of the cited references the Examiner has concluded that it would have been *prima facia* obvious to a person of ordinary skill in the art at the time the invention was made to obtain human, immature dendritic cells, using the method taught by Sallusto *et al.*, and to replace the antigen tetanus toxoid taught by Sallusto *et al.* with a prostate antigen taught by Bigotti *et al.*, for exposure of the prostate antigen to the immature dendritic cells, because the dendritic cells, such as Langerhans' cells, would present prostate antigen to immune cells, and activate specific immune response, and thus, would provide treatment of prostate cancer.

Moreover, the Examiner has asserted that one would have a reasonable expectation of success, because the immature dendritic cells, obtained from culture in GM-CSF and interleukin-4, maintain the antigen capturing and processing capacity characteristics of immature dendritic cells *in vivo*, and efficiently present soluble antigen, as taught by Sallusto *et al.*, and the Examiner has further alleged that because Langerhans cells, which are a type of dendritic cell, are found mainly in low grade prostate cancer, as opposed to the higher grades, and represent a good prognostic indicator, and further because the Langerhans cells are capable of direct prostate antigen presentation to immune cells, and eliciting the immune response, as taught by Bigotti *et al.*

In addition, the Examiner has alleged that it would have been obvious to obtain blood mononuclear cells from a prostate cancer patient for converting to immature dendritic

cells, because the dendritic cells from the prostate cancer patient would be readily available, and would not require donor blood mononuclear cells, and because one would have expected that blood mononuclear cells from a prostate cancer patient would also be able to be converted to immature dendritic cells, using the method taught by Sallusto *et al.*

Still further, the Examiner has asserted it would have been obvious to match the dendritic cells isolated from a normal individual with HLA of the recipient, because dendritic cells, such as Langerhans cells, are directly correlated with HLA class, as taught by Bigotti *et al.*, and thus would not present the antigen with non-matched HLA cells.

The Examiner has conceded that the references do not explicitly teach that the dendritic cells can activate 2 to 3 fold more T cells specific to the prostate antigen as compared to a cell population cultured in the presence of granulocyte- macrophage colony-stimulating factor, interleukin-4, that has not been exposed *in vitro* to the prostate antigen, however, the Examiner has alleged that the immature dendritic cells taught by Sallusto *et al.*, after exposure to a prostate antigen, would present the prostate antigen, and be able to activate 2 to 3 fold more T cells specific to the prostate antigen, because the immature dendritic cells taught by Sallusto *et al.* are produced by the same process as disclosed in the specification of the instant invention, i.e. cultured in the presence of GM-CSF and IL-4. The Examiner believes the claimed dendritic cells to be the same as the dendritic cells taught by the combined art, absent a showing of unobvious differences. Further, the Examiner has stated that as the office does not have the faculties and resources to provide the factual evidence needed in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product in the absence of evidence to the contrary, the burden is on the Applicant to prove that the claimed product is different from those taught by the prior art and to establish patentable differences. See *In re Best* 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and *Ex parte Gray* 10 USPQ2d 1922 (PTO Bd. Pat. App. & Int. 1989).

Applicants must strongly disagree with the Examiner's combination of the cited references. In particular, the Examiner has concluded that the references can be properly

combined and that in combining the teaching of Sallusto *et al.* and Bigotti *et al.* it would have been *prima facia* obvious to a person of ordinary skill in the art at the time the invention was made to obtain human, immature dendritic cells, using the method taught by Sallusto *et al.*, and to replace the antigen tetanus toxoid taught by Sallusto *et al.* with a prostate antigen taught by Bigotti *et al.*, for exposure of the prostate antigen to the immature dendritic cells, because the dendritic cells, such as Langerhans' cells, would present prostate antigen to immune cells, and activate specific immune response, and thus, would provide treatment of prostate cancer.

Bigotti *et al.* do not teach a prostate antigen to replace the tetanus toxoid of Sallusto *et al.* The Examiner has cited to the abstract and to page 85 of Bigotti *et al.* as supporting this conclusion. In actuality, no such statement is found in either the abstract or on page 85 of Bigotti *et al.* or anywhere else in the article. The statement in the abstract that comes closest to the Examiner's contention reads: " . . ., since LCs and HLA class II molecules may provide a means of eliciting the immune response, both LCs and epithelial cells expressing class II molecules being capable of direct antigen presentation to immune cells." The Examiner infers that Bigotti *et al.* teach presentation of *prostate antigen* to the immune system. Applicants respectfully submit that this interpretation of the language in Bigotti *et al.* is not correct and that the Examiner is using Applicants' disclosure to reconstruct the present invention. The teachings of Bigotti *et al.* cited by the Examiner, such as the correlation of LC and tumor grade, the expression of class II molecules by LCs and tumor cells, and the dependence of antigen presenting properties on class II expression, have no bearing on the pending claims, since these characteristics when either considered alone or in any combination, do not infer that human DC exposed *in vitro* to a prostate antigen can activate T cells specific to a prostate antigen, which is the subject matter of the present claims.

In fact, a careful reading of Bigotti *et al.* by one skilled in the art would lead to different conclusions than those set forth by the Examiner. In particular, if in fact the LCs present in the low grade carcinomas were to present prostate antigen to the immune system, one skilled in the art would expect infiltration of immune cells to those locations. Indeed, Bigotti *et al.* examine their histological samples for such infiltrates. (See page 77 bridging to pages 78 and

79). Bigotti *et al.* state "[f]inally we examined all the sections for lymphoid infiltrate, but we found that lymphocytes were scarce in all the tumors, regardless of the degree of differentiation, and were mostly present at the peripheral border of the tumor as small aggregates." "Instead we found that low-grade carcinomas were very rich in HLA class II-positive, interstitial, oval to elongated cells, which were sometimes in close contact with tumor glands (Fig 12), mostly representing macrophages and in only small percentages LCs, as comparing the adjacent S-100-stained section." These results are reviewed in the discussion section found on pages 82-85 of Bigotti *et al.*, where the authors state "[l]astly, we did not find a correlation among cytological grade, HLA-class II expression, LCs, and lymphoid infiltrate as the latter was present mostly at the periphery of tumors as aggregates and did not show close contact with the malignant glands; instead we found a correlation among the aforementioned parameters and the presence of interstitial oval to elongated HLA class II positive cells, interpretable as macrophages, histiocytes, and activated fibroblasts; comparison with the corresponding S-100-stained section showed only a minimal part of these cells corresponded to LCs." The authors' final conclusion was that as there was evidence in the art to support that macrophage play an important roll in tumor rejection, the environment described by their results indicated that a similar mechanism was involved. Clearly, Bigotti *et al.* correlate tumor rejection and lymphocytic infiltrates with the presence of macrophage and not with the presence of LCs. Therefore, the reference would direct the skilled artisan away from combining the references as suggested by the Examiner and towards the use of macrophage to induce immune-mediated tumor rejection.

The Examiner has also asserted that the dendritic cells taught by Sallusto *et al.*, Bigotti *et al.*, and Stites would activate $CD4^+$ and/or $CD8^+$ T cells, because activation of $CD4^+$ and/or $CD8^+$ T cells is a property of dendritic cells, as evidenced by Inaba *et al.* Further, the Examiner has alleged that although the references do not specifically teach that the dendritic cells activate $CD4^+$ and/or $CD8^+$ T cells, the Examiner believes that the claimed dendritic cells are the same as the dendritic cells taught by the combined art, as above, absent a showing of unobvious differences. Based on this conclusion the Examiner has tried to shift the burden onto

the Applicants to prove that the claimed product is different from those taught by the prior art and to establish patentable differences.

The Examiner has not provided a summary or reasoning regarding Stites, but, in order to expedite further prosecution, Applicants will respond to the rejection without commenting on Stites. As above, the Examiner has improperly combined Sallusto *et al.* and Bigotti *et al.* As such, the Examiner has failed to present a proper case of *prima facie* obviousness. There is no teachings provided in any of the cited references that would suggest to the skilled artisan that the dendritic cells taught by Sallusto *et al.*, Bigotti *et al.*, and Stites would activate any T cell, much less $CD4^+$ and/or $CD8^+$ T cells. In fact, as above, Bigotti *et al.* teach the skilled artisan that the immune response against prostate tumor is likely induced by macrophage. This teaches away from the combination of references as constructed by the Examiner.

The Examiner has further noted that although Sallusto *et al.* do not explicitly state that the human peripheral blood is from a normal individual, Sallusto *et al.* do not state that the human peripheral blood is from a diseased individual; and the human peripheral blood taught by Sallusto *et al.* would be expected to be from a normal donor individual. Applicants strongly disagree with the conclusions of the Examiner. As above, there is no disclosure or suggestion in either Sallusto *et al.* or Bigotti *et al.* to replace the tetanus toxoid antigen of Sallusto *et al.* with any other antigen. Bigotti *et al.* do not disclose a prostate antigen or the use of any antigen for *in vitro* contact with any antigen presenting cell. As above, Bigotti *et al.* believe that the immune response observed in their studies likely was induced by macrophage. Therefore, there is no teaching in the combination of Sallusto *et al.*, Bigotti *et al.* and Stites that discloses or suggests the use of normal or "diseased" peripheral blood as a source for dendritic cells.

Claim 24 stands rejected under 35 USC §103(a) as being obvious over Sallusto *et al.* , in view of Bigotti *et al.*, as evidenced by Inaba *et al.*, *supra*, and further in view of Cohen *et al.*, 1994 (*Cancer Res.* 54:1055-1058). The teachings of Sallusto *et al.*, Bigotti *et al.*, and Inaba *et al.* have been set forth above. Further, the Examiner has acknowledged that Sallusto *et al.*,

Bigotti *et al.*, and Inaba *et al.* do not teach that the antigen is a lysate of prostate tumor cells. The Examiner believes that Cohen *et al.* teach that syngenic dendritic cells, when pulsed with tumor lysate, induce antigen-specific proliferation of antitumor $CD4^+$ T cells, relevant to the rejection of the syngenic methylcholanthrene tumor (abstract) and that it would have been obvious to use as prostate antigen, a lysate of prostate cancer cells from a prostate cancer patient, because prostate cancer cells would have several prostate cancer-specific antigens. The Examiner also believes that it would have been obvious to use a tumor lysate because Cohen *et al.* teach that a tumor lysate successfully primes the dendritic cells for inducing antigen-specific proliferation of antitumor $CD4^+$ T cells and the Examiner believes that it would be more convenient to use tumor lysate because it does not require the extra step of purification of the antigen.

As above, the combination of Sallusto *et al.* and Bigotti *et al.* fail to teach the compositions of the present invention. Instead, Bigotti *et al.* teach that macrophage likely induce the immune response seen in prostate cancer. As such, any combination with Inaba *et al.* and/or Cohen *et al.* can not provide the skilled artisan with incentive to combine the references to use a lysate of prostate cancer cells from a prostate cancer patient to make the compositions of the claim 24.

Claim 26 is rejected under 35 USC §103(a) as being obvious over Sallusto *et al.*, in view of Bigotti *et al.*, and as evidenced by Inaba *et al.*, *supra*, as applied to claim 23, and further in view of Lutz *et al.* (of record). The teaching of Sallusto *et al.*, Bigotti *et al.*, and Inaba *et al.* as summarized by the Examiner has been set forth above. Although the Examiner has concluded that Sallusto *et al.*, Bigotti *et al.* and Inaba *et al.* do not teach dendritic cells that are extended life span dendritic cells, the Examiner believes that Lutz *et al.* teach making immortalized dendritic cells (Abstract), which overcomes the problem of being unable to maintain dendritic cells *in vitro* for long periods of time (p. 278). Therefore, the Examiner believes that it would have been *prima facia* obvious to a person of ordinary skill in the art at the time the invention was made to immortalize the dendritic cells taught by Sallusto *et al.*, Bigotti *et al.*, and Inaba *et al.*, using the immortalizing method taught by Lutz *et al.*, because immortalizing

dendritic cells would enable maintenance of dendritic cells *in vitro* for long periods of time, as taught by Lutz *et al.*

As above, the Sallusto *et al.*, Bigotti *et al.* and/or Inaba *et al.* when considered either alone or in combination do not teach the compositions of the present invention. As such, the addition of Lutz *et al.* allegedly teaching immortalization of dendritic cells can not provide the skilled artisan with motivation to make the composition as set forth in claim 26.

Claims 28-29 are rejected under 35 USC §103 as being obvious over Sallusto *et al.*, Bigotti *et al.*, Inaba *et al.*, and Cohen *et al.*, *supra*, as applied to claim 23, and further in view of Taylor *et al.* (of record). The teachings of Sallusto *et al.*, Bigotti *et al.*, Inaba *et al.* and Cohen *et al.* as set forth by the Examiner has been set forth above. Although the Examiner acknowledges that Sallusto *et al.*, Bigotti *et al.*, Inaba *et al.*, and Cohen *et al.* do not teach that the dendritic cells are cryopreserved, the Examiner believes that Taylor *et al.* teach cryopreservation of dendritic cells, wherein said cryopreserved dendritic cells can be used in immunological procedures. As such, the Examiner believes that it would have been *prima faci* obvious to a person of ordinary skill in the art at the time the invention was made to cryopreserve the dendritic cells taught by Sallusto *et al.*, Bigotti *et al.*, Stites (was Inaba *et al.* intended?), and Cohen *et al.*, using the cryopreservation method taught by Taylor *et al.*, to preserve the previously isolated dendritic cells for later use.

As above, Sallusto *et al.*, Bigotti *et al.* and Inaba *et al.*, do not teach the compositions of the present invention. Taylor *et al.* is directed to cryopreservation techniques and does not address the teachings of Bigotti *et al.* Bigotti *et al.* teaches that the immune response is likely induced in prostate cancer by macrophage. As such, Sallusto *et al.*, Bigotti *et al.* and Inaba *et al.*, when considered individually or in any combination does not teach or suggest the composition as set forth in claims 28 and 29.

Claim 30 stands rejected under 35 USC §103 as being obvious over Sallusto *et al.*, Bigotti *et al.*, and Inaba *et al.*, *supra*, as applied to claim 23, and further in view of Taylor *et*

al. (of record), as applied to claim 28, and Lutz *et al.*, (of record). The teachings of Sallusto *et al.*, Bigotti *et al.*, Inaba *et al.* and Taylor *et al.* as set forth by the Examiner have been set forth above. The Examiner has noted that Sallusto *et al.*, Bigotti *et al.*, Inaba *et al.* and Taylor *et al.* do not teach that the dendritic cells have extended life, but the Examiner believes that Lutz *et al.* teach making immortalized dendritic cells (Abstract), which overcomes the problem of being unable to maintain dendritic cells *in vitro* for long periods of time (p. 278). As such, the Examiner believes that it would have been *prima facia* obvious to a person of ordinary skill in the art at the time the invention was made to immortalize the cryopreserved dendritic cells taught by Sallusto *et al.*, Bigotti *et al.*, Inaba *et al.* and Taylor *et al.*, using the immortalizing method taught by Lutz *et al.*, because immortalizing dendritic cells would allow maintenance of dendritic cells *in vitro* for long periods of time, as taught by Lutz *et al.*

As above, the teachings of Sallusto *et al.*, Bigotti *et al.*, Inaba *et al.* and Taylor *et al.* do not disclose or suggest the compositions of the present application. The teachings of Lutz *et al.* when considered either alone or in combination with any of the other cited references does not cure the deficiencies of the primary references, Sallusto *et al.* and Bigotti *et al.* in that Bigotti *et al.* teaches away from the compositions of the present invention.

In view of the above remarks, Applicants respectfully request the Examiner to reconsider and withdraw the various rejections of claims 23, 24, 26, and 28-37 under 35 USC § 103(a) as being obvious over Sallusto *et al.*, Bigotti *et al.* as evidenced by Inaba *et al.*, in view of Stites, and Cohen *et al.*, alone and in various combinations. In particular, Bigotti *et al.* teaches away from the compositions of the present invention by teaching that the immune response to prostate cancer is likely induced by macrophage. In light of the teachings of Bigotti *et al.* the skilled artisan would not have been motivated to produce the compositions of the present invention.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested. If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 206-467-9600.

Respectfully submitted,

Date: 4 December 2006 By: Brian W. Poor

Brian W. Poor
Reg. No. 32,928

TOWNSEND and TOWNSEND and CREW LLP
Two Embarcadero Center, Eighth Floor
San Francisco, California 94111-3834
Tel: 206-467-9600
Fax: 415-576-0300
BWP:jms
60815858 v1